Modern Concepts of Cardiovascular Disease

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GENETIC FACTORS IN CARDIOVASCULAR DISEASES: II. DISORDERS OF PRIMARILY GENETIC ETIOLOGY*†

The disorders, the genetics of which are reviewed in this section, are individually much rarer than those discussed in Part I, but in the aggregate they represent a significant group. They can be classified, somewhat arbitrarily, in the manner shown in Table I.

Several principles relating to these disorders are worthy of emphasis:

1. In most of those listed in Table I, a *single mutant gene*, in either heterozygous ("dominant") or homozygous ("recessive") state, is responsible for the entire syndrome. When seemingly diverse manifestations occur in combination, it is likely that the gene controls some basic biochemical process which has wide implications in the organism.

2. The clinical picture produced by a mutant gene is as *specific* as that produced by a pathogenic microorganism. There is, of course, variability from patient to patient, to be expected in biological phenomena. The other factors in the genetic make-up of the individual and his environment, intra-uterine and extra-uterine, are responsible for the variability in the clinical expression of the mutant gene.

3. Because in embryonic development "many roads lead to Rome," more than one mutant gene may produce what is clinically the same entity. In genetic parlance, this is stated: "In different families, different genotypes may be responsible for a given phenotype." These several genetic forms are mimics of each other. Environmental factors can also result in mimics of genetic

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†Part I of this article, concerned with the four major types of cardiovascular disease, appeared in the July issue.

Table I

Less Common Genetic Disorders with Significant Cardiovascular Implications

Neuromuscular syndromes
- Myotonic dystrophy
- Pseudohypertrophic progressive muscular dystrophy
- Friedreich's ataxia
- Familial periodic paralysis
- Tuberous sclerosis
- Riley's dysautonomia
- Neurocirculatory asthenia

Heritable disorders of connective tissue
- Marfan syndrome
- Pseudoxanthoma elasticum
- Hurler syndrome
- Ehlers-Danlos syndrome

Some myocardial disorders
- Glycogen storage disease
- Familial cardiomegaly
- Hemochromatosis
- Primary systemic amyloidosis

Conduction defects, arrhythmias and ECG variants

Some disorders of blood vessels
- Osler-Rendu-Weber's multiple telangiectasia
- Milroy's disease
- Werner syndrome
- Intracranial "berry" aneurysm

Miscellaneous other disorders

diseases, the so-called phenocopies. The identification of different genotypes is possible when different modes of inheritance are demonstrable in different families: *e.g.*, sex-linked recessive inheritance and autosomal, nonsex-linked, recessive inheritance. The Hurler syndrome, described below, is an example. Differences in linkage relationships, that is, the demonstration that the gene responsible for the disease in one family is located on a different chromosome than the responsible gene in another family, provide evidence of genetic heterogeneity in a condition which is phenotypically homogeneous. Frequently, phenotype differences are detectable when search for them, prompted by demonstration of genotypic differences, is made.

4. Much can be learned about the normal cardiovascular system and about its behavior in acquired disease by the study of rarer heritage disorders. For this reason, genetic disorders often have an importance out of proportion to their numerical frequency.

Neuromuscular Syndromes

Myotonic dystrophy (Steinert's disease) is characterized, in addition to myotonia and muscular dystrophy, by cataracts, temporal balding, gonadal hypofunction and cardiac signs. Cardiac symptoms are rare.[76] Mild cardiomegaly,[76] bundle branch block, especially left bundle branch block, prolonged atrioventricular conduction and diffuse myocardial fibrosis[76, 77] occur. Myotonic dystrophy behaves as an autosomal dominant.[78] Expression is highly variable, even in affected members of the same family, but this is not inconsistent with the single gene hypothesis. Considerable variability of expression is particularly characteristic of "dominant" traits. "Anticipation," progressively earlier onset and more severe disease in successive generations, is probably a statistical artefact resulting from the way cases are detected.[79]

In *pseudohypertrophic muscular dystrophy* of the sex-linked recessive type, the heart is usually involved and this aspect is in some cases an important part of the clinical picture.[80] Cardiac features include progressive cardiomegaly, tachycardia, heart failure, diastolic gallop, muffled heart sounds, arrhythmias, thromboembolic disease, large R waves from the electrocardiographic leads of the right side of the precordium,[81] Q waves simulating those of myocardial infarction and short P-R interval. The walls of the affected ventricle may become very thin. As in hemophilia, only males are affected. The disease usually has its onset in the first decade and runs its course to fatal termination by about the age of 20 years. Myocardial involvement probably is not a feature of the other forms of hereditary muscular dystrophy.

In *Friedreich's ataxia*, in addition to the neurological symptoms, cardiomegaly, T wave changes in the electrocardiogram and functional systolic and diastolic murmurs are found.[82] Pericardial effusion probably occurs in some.[83, 84] The acute rheumatic fever state may be simulated by the motor incoordination, suggesting Sydenham's chorea, frequent complaints of aching in the legs, onset in childhood, and cardiac involvement. Degenerative change in myocardial cells and diffuse myocardial fibrosis are the characteristic anatomical findings.[85] Usually the disease behaves as an autosomal recessive.[86] However, in some families it has the pattern of a dominant, with at least one phenotypic difference, namely, later onset and slower evolution.

In *familial periodic paralysis*, the electrocardiographic changes of hypokalemia accompany the attacks of generalized weakness[87] and cardiac paralysis almost certainly collaborates with respiratory paralysis in causing death. A shift of potassium from the extracellular compartment into muscle cells can be shown[88] to accompany the attacks of weakness, which may be precipitated by heavy carbohydrate intake. The disease sometimes shows the autosomal dominant pattern of inheritance.[89] Interestingly, the same symptoms occur in the rarer *adynamia episodica hereditaria*, which is also inherited as a dominant but in which potassium shifts occur in the opposite direction—from muscle cells to serum.[90] ECG changes of hyperkalemia occur.

Tuberous sclerosis, inherited as an autosomal dominant,[91] has the cardinal features of involvement of the skin (adenoma sebaceum; shagreen skin), of the central nervous system (feeblemindedness; epilepsy), and mixed tumors of the kidney. The lungs are occasionally involved with a form of cystic disease[92] and the myocardium is the site of multiple rhabdomyomata.[93] The myocardial involvement rarely is symptomatic. The tumors, which contain large cells bulging with glycogen, favor the endocardial surface as their location and may produce systolic murmurs by narrowing the outflow tract of one or the other ventricle. ECG changes almost never occur. Rhabdomyomata of the myocardium occur rarely except as part of tuberous sclerosis.[94] Endocardial fibroelastosis has been found.[95]

Also in the category of neuromuscular syndromes with cardiovascular involvement may be mentioned *Riley's dysautonomia*[96] and *neurocirculatory asthenia* (NCA). The genetic features of both are unclear, although the operation of genetic factors seems definite. In Riley's dysautonomia, labile hypertension, suggesting pheochromocytoma, and tachycardia are the main cardiovascular manifestations. The group at the Massachusetts General Hospital[97] have provided data on the familial aggregation of NCA, which is consistent with, although not necessarily indicative of, an important genetic factor, *i.e.*, the proportion of affected siblings varied according

to whether neither parent, one parent, or both parents were affected.

Heritable Disorders of Connective Tissue

The Marfan syndrome, pseudoxanthoma elasticum, and the Hurler syndrome have important cardiovascular features, as may also the Ehlers-Danlos syndrome.[98]

In the *Marfan syndrome*, ectopia lentis and characteristic skeletal proportions (excessively long extremities) occur in combination with an abnormality of the media of the aorta, so that diffuse aneurysm of the ascending aorta, dissecting aneurysm, or a combination of these, develop. The presenting picture is often that of aortic regurgitation, because the first and foremost portion of the aorta to undergo change is the very base. The variability in grade of severity is great and some features of the full syndrome may be missing. The mode of inheritance is probably that of a mendelian dominant; apparently sporadic cases occur rather frequently, however. The aortic abnormality is not a congenital malformation in the usual sense, but rather an inborn weakness of one element of the connective tissue. Deterioration, which may occur early or late, sets in under the influence of the particular hemodynamic stress in the ascending aorta—especially expansile pulsation. Contrary to earlier impressions, conventional cardiovascular malformation, such as septal defects, occurs rarely.

The discovery of a biochemical abnormality will have both diagnostic value and implications for the basic defect. Description of low serum mucoproteins[99] and increased urinary hydroxyproline excretion,[100] although requiring confirmation, are hopeful steps in this direction.

In *pseudoxanthoma elasticum*, degenerative changes develop in the skin of flexural areas, such as the neck, axilla and groin and in the fundus of the eye, where angioid streaks are the characteristic feature. Degeneration and calcification in arteries of intermediate and smaller size lead to massive gastrointestinal bleeding, coronary insufficiency, peripheral vascular insufficiency and hypertension. The age of onset of detected manifestations varies from the first to the fifth decade. There is no agreement as to whether it is elastin or collagen that is defective and undergoes degeneration.[101] Pseudoxanthoma is inherited as an autosomal recessive.

Interesting information on the nature of the basic defect in the *Hurler syndrome* (gargoylism) has become available. Mucopolysaccharide metabolism is deranged.[102] Chondroitin sulfate B and heparitin sulfate are excreted in the urine in considerable quantity. The typical dysostosis with disproportionate dwarfism, the stiff joints and hernia, find ready explanation in a generalized derangement of the ground substance of connective tissue. Mucopolysaccharide deposits in the viscera account for hepatosplenomegaly. Heavy deposits in the coronary arteries, aorta and pulmonary artery and on the heart valves are reminiscent of the atherosclerosis which is produced in rabbits by injections of methylcellulose or pectin.[103] Valvular stenosis and regurgitation, angina pectoris and sudden death result from these deposits. It is possible that in addition to the effects of secondary deposits, the primary mucopolysaccharide abnormality is in part responsible for the valvular changes. The mechanism of the central nervous system change leading to mental deterioration is not clear.

There are two genetic varieties, two genotypes, of the Hurler syndrome and the clinical features, the phenotypes, are slightly different. In one variety, inherited as an autosomal recessive, clouding of the cornea is almost always present and death before the age of 10 years is the rule. In the other variety, inherited as a sex-linked recessive like hemophilia, clouding of the cornea does not occur and survival to a later age is frequent.

The cardinal features of the *Ehlers-Danlos syndrome* are hyperextensibility of joints and unusual hyperelasticity of the skin. The skin is also abnormally fragile. Gaping wounds, which bleed little, however, develop with even minor trauma. Easy bruising is often a presenting complaint. A telltale sign of the disease is the typical cigarette-paper scars of the knees, shins, and other areas of pressure or trauma. The primary fault may be in the way collagen bundles are put together into a wickerwork. The collagen meshwork seems to be loose in the Ehlers-Danlos syndrome.[104] Awaiting confirmation in a larger series, are reports of increased serum elastase inhibitor in two patients with the Ehlers-Danlos syndrome.[105, 106]

I have now collected information on four patients who, in retrospect, seem to have had the Ehlers-Danlos syndrome, who succumbed to dissection and rupture of the aorta at ages ranging from 14 to 24 years. Marked friability of tissues was discovered at autopsy in all and at operation in the three in whom surgery was attempted before death. In two other cases with the Ehlers-Danlos syndrome, pronounced cardiomegaly and murmurs which have not been adequately accounted for are present. The particulars of the cardiac involvement await elucidation.

Some Myocardial Disorders

Since several of the members of this group have been discussed previously in *Modern Concepts*,[107] comments will be restricted largely to the genetic aspects.

There exist probably at least four types of *glycogen storage disease*, representing distinct entities clinically, pathologically, chemically and

almost certainly genetically. In only one form is cardiac involvement significant.[108] Von Gierke's disease, in which the liver and kidney are involved predominantly, occurs more frequently than the cardiac form. (Of the two other very rare forms, hepatic deposition of abnormal polysaccharide with severe cirrhosis is the feature of one, and limitation of glycogen deposition largely to skeletal muscle is the feature of the other.) Macroglossia and weakness and hypotonia of skeletal muscle occur in some cases of the cardiac form. The cardiac form is inherited as an autosomal recessive. Parental consanguinity is frequent. The affected infant usually does not survive to an age of more than a few months. Only about 24 cases are recorded in the entire literature.[109]

In recent years, several reports of *familial cardiomegaly*[110-112] familial cardiomyopathy, idiopathic cardiac hypertrophy,[113] asymmetrical cardiac hypertrophy, and so on, have accumulated. The features have been cardiomegaly, arrhythmias, conduction defects, heart failure, and sudden or unexpected death at a relatively early age in multiple members of families. The pathological picture has been patchy fibrosis and hypertrophy of the myocardium. It is highly probable that we are not dealing with a single etiological and pathogenetic entity.

As demonstrated by Brigden,[114] there are on record at least eight instances in which a mother and one or more of her children were affected. Instances in which a father and children were affected are difficult to find in the literature. The possibility that the familial aggregation is due to congenital infection and not genetic determination must be given serious consideration. In addition to the classic prototype, congenital syphilis, toxoplasmosis and cytomegalic inclusion disease are passed from mother to child. Furthermore, toxoplasmosis can produce fatal myocarditis.[115] The cases of toxoplasma myocarditis identified to date have presumably had recently acquired disease. However, experience with ocular toxoplasmosis would suggest that the disease acquired by placental transmission may flare up periodically in later extrauterine life.

The genetics of *idiopathic hemochromatosis*, in which myocardial involvement is an important feature, is unclear.[116] Lamy[117] suggests that it is an autosomal recessive with expression much reduced in the female because of the "safety valve" of menstruation. It seems likely that this disorder will prove to be an inherited defect in the control of iron absorption and/or transport. Kappeler[118] described three brothers with familial cardiomyopathy on the basis of hemochromatosis.

Familial systemic primary amyloidosis is inherited in both mice[119] and man.[120] There may be more than one variety of systemic amyloidosis; in most instances there are no other affected members of the family. A thorough family study, starting with a sizable group of probands, is required.

Conduction Defects, Arrhythmias and Electrocardiographic Variants

Bundle branch block,[121] complete heart block,[122] the Wolff - Parkinson - White syndrome,[123] atrial fibrillation[124] and paroxysmal supraventricular tachycardia occur sufficiently often in multiple members of the same family to make it likely that such aggregation is not mere coincidence. On the other hand, "familial cases" do not occur frequently enough to be of diagnostic help or concern in the management of patients and their families; they are certainly not seen so often that a simple genetic hypothesis could be formulated.

It is known from twin studies that inheritance is a factor in the general pattern of the electrocardiogram.[125-128] Electrocardiographic peculiarities of the Negro, specifically late persistence of the juvenile pattern of T waves, is well recognized.[129-130] That family or twin studies will indicate a genetic basis is likely.

Recently, a puzzling syndrome[131] of congenital deaf-mutism, prolonged Q-T interval, and sudden death has been described in siblings.[132]

Some Disorders of Blood Vessels of Intermediate and Smaller Size

In a small but significant proportion of cases of *Osler-Rendu-Weber's multiple telangiectasia*, pulmonary arteriovenous fistulae occur. Telangeictases on the inner aspect of the lip, tip of the tongue, conjunctivae and elsewhere may go unnoted unless specifically sought. Over half of all cases of pulmonary arteriovenous fistula have the Osler-Rendu-Weber disease.[133] Aneurysms of the splenic artery have been described.[134] Osler-Rendu-Weber's disease is inherited as an autosomal dominant. Most affected persons are, of course, heterozygotes. Snyder and Doan[135] described a severely affected newborn infant, the offspring of two mildly affected parents, who may have been homozygous for this dominant trait.

Milroy's hereditary lymphedema is inherited as an autosomal dominant.[136] Kinmonth, *et al.*[137] found that there were other affected members in the families of 18 of 107 patients with lymphedema of congenital or early onset. Although, as the name suggests, the disease has been thought to represent a congenital malformation of the lymphatics, histological peculiarities of the arterioles and high blood flow in the legs, as indicated by elevated skin temperature, persistent relative tachycardia, high cardiac output and low femoral arteriovenous oxygen difference,[138] have suggested that the defect is in the arterioles. In this view, failure of the arterioles

to contract properly results in "filtration edema."[139] The old observation[140] of low arteriovenous oxygen difference in leg edema of diverse origins and the rise to the normal range with diuresis[141] makes the "arteriolar theory" unlikely. The high flow is probably a variety of "reactive hyperemia."

In the *Werner syndrome*,[142] determined by a genetic factor which may be autosomal recessive, scleroderma-like skin changes and cataracts are leading features. Peripheral vascular disease with arterial insufficiency can be a striking feature.

Varicose veins clearly "run in families."[143, 144] The genetics is complicated. Non-genetic factors, such as occupation and pregnancy, are of obvious importance. A genetically determined defect of the wall of the great saphenous vein in the valve area at the saphenofemoral junction has been suggested.[145]

Intracranial "berry" aneurysm has been reported in multiple members of families.[146] We have seen aneurysm of the *left* internal carotid artery as the cause of death in both a 34 year old man and his 13 year old daughter. Intracranial aneurysm is rather frequently associated with hereditary cystic disease of the kidneys.[147, 148] Aneurysm may be one of the pleiotropic effects of the same "dominant" gene, which results in the renal malformation.

Miscellaneous Other Disorders

Buerger's *thromboangiitis obliterans*, reported rather frequently in multiple members of the same family and which is probably more frequent in Jews,[149] is currently under critical scrutiny to determine whether it is an entity distinct from ordinary peripheral arteriosclerosis.[150] Lewis and Pickering[151] described a large family in which many members of several generations had *Raynaud's disease*. Quincke's *angioneurotic edema* is, in a sense, vascular in nature. It is inherited as an autosomal dominant.[152] I have seen it in at least six members of three generations with death from laryngeal obstruction in the person of the first generation. *Ankylosing spondylitis*, frequently accompanied by aortic regurgitation, shows a strong familial tendency.[153] *Systemic lupus erythematosus* demonstrates some familial aggregation;[154] whether this aggregation is genetic in its basis is not clear. In *alkaptonuria*, the deposit of ochronotic pigment in the heart valves incites scarring and calcification,[155] just as its deposit in the intervertebral cartilages results in calcifying and ankylosing changes. *Obesity*, a factor in cardiovascular disease, is probably under partial genetic control,[156] although the details are unclear. Cor pulmonale develops secondary to several hereditary disorders of the lung: *cystic disease of the lung*,[157] *idiopathic pulmonary fibrosis*, and the chronic lung disease of *cystic fibrosis of the pancreas*.[158] In various forms of *hereditary anemia* (sickle cell anemia, thalassemia major, hereditary spherocytosis, Fanconi's familial hypoplastic anemia) cardiac manifestations may be striking and confusing.[159] Smith and Conley[160] described an 11 year old boy with the sickle cell *trait* and tetralogy of Fallot. The patient had hemolytic anemia because of the association of reduced oxygen tension with the sickling propensity. His anemia was corrected by the Blalock-Taussig operation.

It should be evident from the survey in this and the preceding issue of *Modern Concepts* that the genetic background can be an important etiological factor in cardiovascular disease.

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REFERENCES

Space does not permit the publication of the references included in Parts I and II of this article. A complete list of references is available, on request, from the *Author* or from the *Membership Section of the American Heart Association.*